The SAATELLITE and EVADE Clinical Studies Within the COMBACTE Consortium: A Public–Private Collaborative Effort in Designing and Performing Clinical Trials for Novel Antibacterial Drugs to Prevent Nosocomial Pneumonia

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The Innovative Medicines Initiative–funded COMBACTE consortium fosters academic-industry partnership in pioneering studies to combat serious bacterial infections. We describe how this partnership is advancing the development of 2 monoclonal antibodies, MEDI4893 and MEDI3902, for the prevention of nosocomial pneumonia.

Keywords. nosocomial pneumonia; ventilator-associated pneumonia; monoclonal antibody; ICU.

Bacterial pneumonia, especially that occurring within the hospitalized or intensive care unit (ICU) population, is a clinically relevant and serious disease caused by both antibiotic-resistant and -susceptible strains. The infection contributes significantly to morbidity and mortality, increases ICU and hospital length of stay, and represents a substantial economic burden [1, 2]. In the United States and Europe, nosocomial bacterial pneumonia, or hospital-acquired pneumonia (HAP), constitutes one of the leading nosocomial infections [3, 4], despite numerous guidelines, international recommendations, and increasing adoption of ventilator-associated pneumonia (VAP) prevention care bundles—a series of interventions related to ventilator care that, when implemented together, will achieve significantly better outcomes than when implemented individually [5, 6]. Mechanical ventilation (MV) is the most significant risk factor for nosocomial pneumonia [7–13]. VAP, defined as pneumonia occurring >48 hours after patients have been intubated and received MV, is reported to affect up to 28% of patients on MV [4], with a reported attributable mortality of 13% [14].

In addition to the VAP care bundles and other prevention approaches (oral decontamination, weaning protocols, sedation holidays, etc), current VAP management consists mainly of antibiotic treatment once there is disease progression. Both *Staphylococcus aureus* (*Sa*) and *Pseudomonas aeruginosa* (*Pa*) are the bacteria most frequently responsible for VAP [15, 16], and *Pa* is one of the most adaptive in developing multidrug resistance [4]. The loss of effective antibiotics undermines the ability to manage complications due to infections in vulnerable patient populations, including critically ill patients. However, novel antimicrobial agents and real-time diagnostic techniques have the potential to modify the management of VAP in the ICU and could soon result in new preventive approaches [17].

HAP/VAP DIAGNOSTIC ISSUES

Across the many commonly used definitions for VAP, it is generally agreed that VAP should be diagnosed using a combination of clinical, laboratory, radiographic, and microbiological criteria; however, diagnosing VAP remains problematic due to the lack of sensitivity and specificity of these criteria. For example, interpretation of chest radiographs is inherently variable, and some of the specific clinical signs and symptoms are subjective and may be inconsistently documented. Therefore, the distinction between asymptomatic carriage of bacteria in the respiratory tract and symptomatic bacterial infection is difficult, often leading to faulty assessments that impact the validity and

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reliability of surveillance data and clinical trial findings. As a result, a number of different approaches have been proposed to improve surveillance processes [18–21]. In addition, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have developed guidance aimed at standardizing therapeutic approaches and harmonizing HAP/VAP definitions and endpoints for industry-sponsored clinical trials [22–24].

CURRENT PROPHYLAXIS AND PREEMPTIVE APPROACHES IN HAP/VAP

None or very few other prophylactic strategies show definitive effectiveness in the real-world environment. The systematic prophylactic use of antibiotics to prevent VAP can be associated with some adverse consequences such as emergence of resistance [18]. In patients nasally colonized with *Sa*, mupirocin reduces bacterial carriage, but its direct impact on VAP incidence remains to be clearly demonstrated and resistance to this compound has been reported [25]. Selective digestive decontamination and selective oropharyngeal decontamination effectively reduce the incidence of VAP [26] and improve patient outcome in settings with low levels of antibiotic resistance [27–29]; however, there is uncertainty as to whether these beneficial outcomes can be achieved in settings with high levels of antibiotic resistance. The use of the oral antiseptic chlorhexidine has been shown to decrease the incidence of VAP with favorable safety profile and cost considerations [30], cardiac patients possibly benefiting the most [31]. The use of specific endotracheal tubes has shown conflicting results on VAP incidence and tracheal colonization, and therefore, these also remain an unproven strategy [32].

NOVEL PROPHYLACTIC AND PREEMPTIVE STRATEGIES IN HAP/VAP

A move toward innovative prevention approaches that employ novel anti-infective agents could enable a change from the current "late treatment approach" paradigm and decrease the use of antibiotics. Preemptive strategies targeting a well-defined population at higher risk of HAP/VAP could be an intermediate approach between early antibiotic prophylaxis, which will increase antimicrobial resistance selection pressure, and delayed treatment, which may worsen clinical outcomes. Because colonization of the upper and lower respiratory tract in ICU patients on MV precedes the development of infection in all cases [33–35], this population is an ideal target for preemptive strategies given before the clinical manifestations of pneumonia become evident.

Probiotics could be used as prophylaxis, but trials with positive results were underpowered to make this conclusive [36]. Appropriate antibiotherapy when given in cases of ventilator-associated tracheobronchitis (VAT) may decrease the incidence of VAP [37]. Aerosolized adjunctive therapy using antibiotics (even started prophylactically) could also represent an interesting alternative option to intravenous antibiotics in VAT [38, 39]. As another approach, several vaccines are being evaluated in the ICU population, but such a preventive approach has yet to be shown efficacious [40].

POTENTIAL BENEFIT OF MONOCLONAL ANTIBODIES FOR MANAGING NOSOCOMIAL INFECTIONS

Because antibiotic options for the treatment of infections caused by multidrug-resistant bacteria are more and more limited, there is a medical need for treatment approaches that are independent of antibiotic susceptibility. In the continuing effort to identify viable alternatives, antibodies (Abs) are emerging as a potential choice. Monoclonal antibodies (mAbs) represent an attractive alternative to antibiotics, for either prophylaxis or preemptive therapy, because of their safety profile, specificity, mechanism of action, long half-life, and potential to reduce antibiotic use. Investigational mAbs have already been used successfully in the ICU as adjunctive therapy in patients with *Pseudomonas* VAP [41] with a positive signal on clinical resolution. The first trial evaluating the preemptive use of an mAb targeting PcrV in *Pa* yielded a decrease in the incidence of infectious events in patients on MV [42].

PUBLIC–PRIVATE PARTNERSHIPS FOR NEW ANTIBACTERIAL STRATEGIES

The Combatting Bacterial Resistance in Europe groups (COMBACTE-NET for gram-positive infections and COMBACTE-MAGNET for gram-negative infections) are 2 consortia of 8 pharmaceutical industry partners and 51 academic partners (to date) that have evolved as part of a project developed under the Innovative Medicines Initiative to address the concerns of increased antibacterial resistance [43]. The focus of these consortia is to design and implement clinical trials specifically in the area of HAP/VAP, including preventive and novel therapeutic approaches and investigation of novel agents that have the potential to treat multidrug-resistant pathogens. Within these consortia, COMBACTE CLIN-net and COMBACTE LAB-net are the networks that focus on clinical and laboratory research, respectively. Thus, the consortia bring together those who are in the forefront in their area of expertise, allowing for the conduct of high-quality research in the areas of epidemiology, prevention, and treatment of infections.

SAATELLITE AND EVADE STUDIES AND DESIGN CONSIDERATIONS

Two trials are currently under way within COMBACTE to evaluate the benefits of mAbs in ventilated subjects at risk for developing *Sa* or *Pa* pneumonia (Table 1). MEDI4893, an mAb that binds *Sa* alpha toxin (AT) and prevents AT pore formation in target cell membranes [44], is being studied in the SAATELLITE (A Human Monoclonal Antibody Against *Staphylococcus aureus*

Table 1. Efficacy Endpoint of Nosocomial Pneumonia in the Clinical Trials Using MEDI4893 and MEDI3902

Endpoint	SAATELLITE Study (MEDI4893) (A Human Monoclonal Antibody Against *Staphylococcus aureus* Alpha Toxin in Mechanically Ventilated Adult Subjects)	EVADE Study (MEDI3902) (Effort to Prevent Nosocomial Pneumonia Caused by *Pseudomonas aeruginosa* in Mechanically Ventilated Subjects)
Trial	A phase 2 randomized, double-blind, placebo-controlled, single-dose, dose-ranging study of the efficacy and safety of MEDI4893, in MV adult subjects colonized with *Sa*.	A phase 2 proof-of-concept study to evaluate the efficacy and safety of MEDI3902 in MV colonized patients for the prevention of nosocomial pneumonia caused by *Pa*.
Primary efficacy endpoint	The incidence of *Sa* pneumonia through 30 d after a single dose of MEDI4893 in MV subjects at risk for *Sa* pneumonia.	The incidence of nosocomial pneumonia caused by *Pa* through 21 d postdose after a single dose of MEDI3902 in MV subjects at risk for *Pa* nosocomial pneumonia.
Definition of MV and non-MV	*MV:* Subject is intubated with an endotracheal or nasotracheal tube and receiving positive pressure ventilation support, or subject is not intubated with an endotracheal or nasotracheal tube, but requires ≥8 h of positive pressure ventilation. *Non-MV:* Not mechanically ventilated is defined as not having an endotracheal or nasotracheal tube or requiring positive pressure ventilation support for at least 8 h.	
Radiological, clinical, and microbiologic criteria to be met concurrently for the endpoint of pneumonia in MV and non-MV Subjects	*Radiographic confirmation for both MV and non-MV subjects:* New or worsening infiltrate consistent with pneumonia on chest radiograph obtained within 24 h of the event (diagnosed by a qualified radiologist). *Clinical confirmation for MV subjects:* At least 2 of the following minor or 1 major sign or symptoms of new onset: • *Minor criteria*: (1) systemic signs of infection (1 or more of the following): abnormal temperature and/or abnormal WBC count; (2) production of new purulent endotracheal secretions; (3) new physical examination findings consistent with pneumonia/pulmonary consolidation. • *Major criteria*: acute changes made in the ventilatory support system to enhance oxygenation, as determined by partial oxygen pressure. *Clinical confirmation for non-MV subjects:* At least 2 of the following minor or 1 major signs or symptoms: • *Minor criteria*: (1) systemic signs of infection: Abnormal temperature and/or abnormal WBC; (2) a new onset of cough (or worsening of cough); (3) production of purulent sputum; (4) physical examination findings consistent with pneumonia/pulmonary consolidation; (5) dyspnea, tachypnea, or hypoxemia. • *Major criteria*: a need to initiate noninvasive mechanical ventilation or reinitiate invasive mechanical ventilation because of respiratory failure or worsening of respiratory status. *Microbiologic confirmation for MV subjects:* At least 1 of the following obtained within 24 h of onset of the event: • Lower respiratory specimen positive for *Sa* (for SAATELLITE) and *Pa* (for EVADE) by culture. • Blood culture positive for *Sa* (for SAATELLITE) and *Pa* (for EVADE) (and no apparent primary source of infection outside the lung). • Pleural fluid aspirate or lung tissue culture positive for *Sa* (for SAATELLITE) and *Pa* (for EVADE) during episode of pneumonia (only if obtained as part of the subject's necessary clinical management). *Microbiologic confirmation for non-MV subjects:* Same as MV subjects but respiratory sample to also include expectorated sputum; a culture may be obtained within 72 h of onset of the event.	

Abbreviations: MV, mechanically ventilated; *Pa, Pseudomonas aeruginosa*; *Sa, Staphylococcus aureus*; WBC, white blood cell.

Alpha Toxin in Mechanically Ventilated Adult Subjects) study. MEDI3902, a bivalent bispecific mAb that selectively binds to both the PcrV protein and Psl exopolysaccharide on the surface of *Pa*, is being studied in EVADE (Effort to Prevent Nosocomial Pneumonia Caused by *Pseudomonas aeruginosa* in Mechanically Ventilated Subjects). Binding to PcrV on intact *Pa* blocks type 3 secretion injectisome-mediated cytotoxicity and damage to host cells. Binding to Psl mediates opsonophagocytic killing of *Pa* by host effector cells and inhibits *Pa* attachment to host epithelial cells [45]. The preventive modalities of both Abs are such that they could supplement the current standard of care for the prevention of nosocomial pneumonia, including other infection control practices.

Designing prevention studies is particularly challenging as these are new territory for antimicrobial drug development. EMA and FDA guidance for the development of products intended to treat nosocomial pneumonia are available and have been considered in designing the clinical studies for MEDI4893 and MEDI3902 [22, 23, 46]; however, these documents provide limited guidance for developing prophylactic medicines intended to prevent nosocomial pneumonia. As such, early input from both EMA and FDA was essential to the trial designs, definitions, and clinical endpoints.

UNIQUE ASPECTS OF THE STUDIES AND STUDY CONDUCT

Consultation Process in the Collaboration

One of the strengths of the COMBACTE consortium is that it merges expertise and capabilities from basic science and clinical research experts in the field of infectious disease and critical care, thereby optimizing the interaction of experts. Accordingly, instead of the traditional study designed by a sponsor, with limited scientific input through advisory boards, both SAATELLITE and EVADE have been built by a working group within the consortium, including not only the clinical experts and the Sponsor (MedImmune), but also microbiologists to take advantage of this innovative public–private partnership to address several important microbiological, clinical, immunological, biological, and biomarker questions.

Selection of Endpoints That Are Clinically Meaningful and Reproducible

Whereas clinical resolution of the infection and reduction in mortality remain the standard primary endpoints in the classical noninferiority VAP treatment trial, prevention of the onset of VAP is proposed as a preemptive approach using mAbs. To conduct meaningful clinical trials, MedImmune and COMBACTE partners had to develop and adapt existing definitions for VAP diagnosis to a definition of *Sa* and *Pa* pneumonia for the primary endpoint assessment. The definition was based on objective and reproducible clinical, laboratory, radiographic, and microbiologic criteria, and was meant to be reproducible and consistently implemented by all investigators participating in the efficacy studies. The primary efficacy endpoint of nosocomial pneumonia and its definition are shown in Table 1.

While all study subjects will be on MV at the time of enrollment and a substantial number of subjects will likely continue to require MV throughout the postdose period, some will be successfully weaned during this period but may still develop pneumonia after extubation. Therefore, primary efficacy will be evaluated in subjects who remain on MV as well as those extubated and no longer requiring MV through the follow-up periods of 30 and 21 days for MEDI4893 and MEDI3902, respectively.

In both studies, pneumonia will be identified at the bedside by the physician responsible for the subject, but every event will then be confirmed by an endpoint adjudication committee. This committee—consisting of an independent group of experts selected by the COMBACTE consortium, including the sponsor—will review blinded data reported by trial investigators to determine whether the endpoints meet protocol-specified criteria.

With approximately 900 subjects targeted in both SAATELLITE and EVADE, secondary endpoints should generate a large volume of information that may benefit future programs. These trials, coupled with an epidemiology ASPIRE study (Advanced Understanding of *Sa* and *Pa* Infections in Europe), also conducted within the COMBACTE consortium, will generate data on *Sa* and *Pa* colonization in patients on MV that should advance our knowledge in treating patients.

Use of Real-time Techniques to Detect Colonization

For both trials, a species-specific real-time diagnostic assay will be used to screen for *Sa* or *Pa* colonization before onset of any infection. Endotracheal aspirate will be screened by polymerase chain reaction for *Sa* or *Pa*, respectively, using *Sa*- or *Pa*-specific tests developed by Cepheid Diagnostics (Sunnyvale, California) [47]. These rapid molecular diagnostics require <5 minutes of hands-on time, can be performed routinely and easily (even potentially at the bedside), and have been developed to identify colonized patients. The *Sa* test identifies both methicillin-susceptible and methicillin-resistant *Sa* using an existing skin and soft tissue infection test system that has been adapted for use with lower respiratory tract samples. Within 90 minutes of sampling, respiratory tract colonization with *Sa* or *Pa* is confirmed. This is the first time that a complementary rapid diagnostic is being used to identify colonized patients in the ICU in a VAP prevention trial. With the rapid advances in molecular biology and instrumentation, these assays could pave the way for a new paradigm in identifying high-risk patients and providing prophylaxis or preemptive treatment for other serious bacterial infections such as *Acinetobacter baumannii* and *Klebsiella pneumoniae*.

Ancillary Biomarker Program

The COMBACTE consortia programs also offer a unique opportunity to help characterize pathogen virulence factors, the host immune system, and other host factors that facilitate pathogen-induced disease and/or play a role in the host response to colonization and infection. Establishing a comprehensive biomarker strategy, as ancillary research studies to SAATELLITE and EVADE, is a cornerstone of this public–private consortia, and translational, epidemiological, and basic research performed by some of the leading laboratories in Europe will generate new insights into the host–pathogen relationship and provide new knowledge for future antibiotic, mAb, and vaccine development. In both studies, the opsonophagocytic killing activity in serum and serum Abs against bacterial virulence factors will be measured. In SAATELLITE, this includes measuring AT-specific serum immunoglobulin G (IgG) and AT serum neutralizing Abs, as well as a panel of 75 other virulence factors of *Sa*. Subsequently, more in-depth immunological and clinical analyses will be performed to determine correlates of protection. This includes characterizing the complete immune-proteome against all *Sa* antigens with select samples by 2Dgel/Western blot analysis. An in-depth analysis of Abs against nonprotein cell wall structure quantification of the contribution of the 4 IgG-evasion molecules (SpA, SSL10, SBI, and FLIPr) will be performed. For EVADE, serum Ab levels against PcrV and Psl will be performed at baseline and over time in subjects with and without microbiologically confirmed *Pa* infection. Levels of Psl and PcrV will be characterized on *Pa* isolates from the EVADE study, and the levels of secreted AT will be determined on methicillin-susceptible and methicillin-resistant *Sa* isolates from the SAATELLITE study. In both the SAATELLITE and EVADE clinical studies and the ASPIRE epidemiology study, a complete antibiogram will be performed on the isolates to gain a better understanding of the incidence and prevalence of antibiotic resistance in ICUs, and whole-genome sequencing of *Sa* and *Pa* will be performed to fully characterize the resistome and toxome of the bacterial species. Last, levels of host inflammatory biomarkers in blood, serum, and respiratory samples will be determined to identify patients at greatest risk of developing pneumonia, sepsis, or other complications from bacterial colonization or infection.

CONCLUSIONS

The standard of care for prevention of *Sa* and *Pa* infection in patients on MV relies primarily on the implementation of hospital

infection control methods, which historically have been shown to produce varying levels of sustained success, never reaching complete prevention or control. Adaption of new preventive modalities, such as pathogen-specific mAbs, may augment success rates, but will require a shift in the strategy of treating and managing high-risk patients to prevent serious *Sa* and *Pa* infections.

Notes

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